

REMARKS

Claims 14 and 16-22 are pending in this application.

I. Examiner's Position

Preliminary Issues

The Examiner contends that the English translation of the abstract of WO 93/15199 is insufficient and that Applicants should submit a concise statement of the relevance of the reference. Applicants submit herewith a translation sufficient to explain the disclosure of a reference.

Rejection under 35 U.S.C. 103

The Examiner maintains the rejection of claims 14 and 16-22 as unpatentable under 35 U.S.C. 103(a) and issues new grounds for this rejection.

A. Old Ground for Rejection Maintained

The Examiner maintains the rejection of claims 14 and 16-22 as unpatentable under 35 U.S.C. 103(a) over Delgado *et al.*, *British J. Cancer* 73:175-182 (1996) in view of U.S. Patent 5,714,142, WO 98/00171, U.S. Patent 5,670,132 and Peters (that was previously encountered).

Alleged *prima facie* case of obviousness

The Examiner maintains that it would have been obvious to **1) substitute the PEG** of the antibody fragment of Delgado *et al.* **with the albumin** of the '142 patent and WO 98/00717. Moreover, it would have been obvious to have **2) linked the antibody fragment to albumin using a linker such as an optionally substituted hexylene** as taught by the '142 patent **or the 6 carbon alkylene** linker of WO 98/00717. Further, such linker would have been **3) linked via the thiol at the free cysteine in albumin** as taught by Peters, and the thiols would have been created as per the '132 patent to have **4) optionally linked the conjugate to a label** (in effect the reporter group of claim 19 of the present application).

Motivation to make such changes

The Examiner continues to maintain that **1)** one of skill in the art would have been motivated to **increase the efficacy of drug delivery or tumor imaging** by increasing antigen binding capacity and half life of a subject antibody fragment by linking it to albumin via a linker. The Examiner adds that **2)** the '142 patent and WO 98/00717 teach proper linkers (optionally substituted hexylene or 6 carbon alkylene). Moreover, the Examiner adds that **3)** Peters teaches free cysteine in albumin and that it would be **obvious to couple albumin at this cysteine because this cysteine is available without requiring manipulation or causing a conformational change in albumin**. Further, the Examiner maintains that **4)** the '132 patent teaches that **reduced cysteine residues (i.e. thiol) in the hinge region of antibody fragments may be used to label antibody fragments**.

The Examiner's response to Applicant's previous arguments

The Examiner makes the following comments regarding Applicant's previous arguments:

1. The number of references combined in the obviousness rejection is not dispositive.
2. The Delgado *et al.* reference is analogous art. Delgado *et al.* teach that the PEGylated antibody can be optimized for maximum retention of antigen binding via PEGylation in the presence of antigen to mask the binding site, ie., that PEGylation with more than one PEG molecule obscures or otherwise interferes with the antigen binding site of the antibody and so does provide motivation to make changes to the construct. The Examiner admits that Delgado *et al.* do not provide any motivation to substitute albumin for PEG, however, the Examiner says that the '142 patent teaches that albumin inhibits renal clearance as does PEG.

3. The '142 patent does not teach away from coupling albumin to an antibody because the '142 patent teaches coupling albumin to peptides, proteins or other drugs for increasing half life by inhibiting renal excretion.
4. WO 98/00717 teaches that albumin covalently coupled to drugs extends the half life of the drugs. Moreover, it teaches away from using hydroxyl groups to link drugs to albumin.
5. One of ordinary skill in the art would have been motivated to use the free thiol at position 34 of albumin for coupling because no intra-chain disulfide bonds would be disrupted. Moreover, WO 98/00717 teaches that drugs may be conjugated to albumin via a hexylene linker at a thiol group to increase half life.

B. New Ground for Rejection

The Examiner rejects claims 14 and 16-22 as unpatentable under 35 U.S.C. 103(a) over Delgado *et al.*, *British J. Cancer* 73:175-182 (1996) in view of U.S. Patent 5,714,142, WO 98/00171, U.S. Patent 5,670,132, Peters (that was previously encountered) and WO 93/15199.

The Examiner reiterates his characterization of the references and adds that WO 93/15199 teaches recombinant peptides comprised of albumin (including human albumin) and a therapeutically active polypeptide such as an antibody or portion of an antibody.

Alleged *prima facie* case of obviousness

The Examiner maintains that it would have been obvious to substitute the albumin of the '142 patent and WO 98/00717 for PEG in the antibody fragment conjugate of Delgado *et al.*, such as in the recombinant albumin-antibody polypeptide taught by WO 93/15199. In contrast to WO 93/15199, it would have been obvious to have linked the antibody fragment rather than genetically fusing it to albumin using a linker such as the hexylene of the '142 patent or the 6

carbon alkylene of WO 98/00717. Further, it would have been obvious that such linker would have been linked via the thiol at the free cysteine in albumin as taught by Peters, and the thiols would have been created as per the '132 patent to have optionally linked the conjugate to a label (in effect the reporter group of claim 19 of the present application).

Motivation to make such changes

The Examiner reiterates the motivation outlined above and adds that one of skill in the art would have been motivated to link rather than genetically fuse the albumin to the antibody as such linking is taught by WO 93/15199.

As regards claim 17, the Examiner contends that it would have been obvious to extend the fab at the CH₁ carboxy terminus to include the cysteine involved in the interchain disulfide bond of the intact antibody in order to use the cysteine in disulfide binding without disrupting intrachain disulfide bonds. Moreover, the '132 patent allegedly teaches introducing additional thiol groups to the bivalent F(ab')₂ and F(ab)₂ fragments.

Telephone Interview

On February 9, 2006 Applicant's attorney, J. David Smith, spoke with the Examiner telephonically. The Examiner recommends submitting evidence of patentability, such as, for example, one or more of the following:

1. Technical explanations regarding any difficulties encountered making the conjugate molecule; or
2. Technical explanations regarding why the antibody would not be expected to maintain its binding affinity with the linker and albumin; or
3. Technical explanations as to why the particular linker would not be expected to be effective as used between the particular cysteine residues; or

4. Comparative data demonstrating that the particular linker provides unexpectedly superior length of half life or preservation of binding affinity compared to a conjugate using another linker; or
5. Comparative data demonstrating that an albumin conjugate provides unexpectedly superior length of half life compared to an unconjugated antibody.

II. Applicant's Response

A. The Examiner has not set forth a proper *prima facie* case of obviousness

Applicants respectfully remind the Examiner that in order to establish a proper *prima facie* case of obviousness, the Examiner must establish certain criteria as follows:

1. That there is a **suggestion or motivation to modify the references** or to combine the reference teachings;
2. **There must be a reasonable expectation of success**; and
3. The references or combination of references must teach or suggest all of the claim limitations (*see, e.g.*, MPEP § 2142).

The teachings or suggestions to make the claimed combination and the reasonable expectation of success must both be found in the prior art and not based on applicant's disclosure (In re Vaeck, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991)). The arguments advanced by the Examiner fail to meet all of these criteria.

The law is settled that prior to combining references for the purpose of determining obviousness, “there must be some objective teaching in the prior art or knowledge generally available to one of ordinary skill in the art that would lead that individual to combine the relevant teachings of the references.” *See, In re Fine*, 837 F.2d 1071, 1074, 5 U.S.P.Q.2d 1596, 1598 (Fed. Cir. 1988).

The law is also settled that “the prior art references must be evaluated on what they taught or suggested...when the invention was made, not on hypothetical modifications made with knowledge of the invention...” (*See, e.g. Interconnect Planning Corp. v. Feil*, 774 F.2d 1132, 1138, 227 U.S.P.Q. 543, 547 (Fed. Cir. 1985)) The Examiner’s rejection appears to be based purely on hindsight, and hindsight has never been permissible to establish a *prima facie* case of obviousness. The fact that the Examiner is combining sections from no less than four documents to arrive at the subject-matter of claim 14 demonstrates, in itself, that the invention is not obvious as the Examiner alleges. Furthermore, the Examiner’s allegation that motivation to combine these documents exists within the documents is incorrect, as shown by the detailed review of the documents provided below.

B. No motivation to combine references

In view of the content of the cited references, it is apparent that the skilled person would have had no motivation to combine the references in the manner suggested by the Examiner.

1. No motivation to replace PEG with single albumin

There was no problem associated with attaching several PEG molecules to an antibody fragment in Delgado *et al.* or the ‘132 patent. The approaches described therein were apparently successful and there would have been no motivation for replacing PEG with a single albumin. Importantly, there is no evidence or suggestion in any of the references cited, in particular the ‘142 patent and the ‘171 patent, that substituting PEG for albumin would increase the ‘antigen binding capacity’ of an antibody fragment as asserted by the Examiner. The ‘142 patent is concerned with linking drugs to TTR *in vivo*, not with covalently conjugating albumin to an antibody fragment *in vitro*. The ‘171 patent makes no reference to antibodies but relates to randomly attaching several thrombin inhibitors to albumin.

2. **No motivation to use linkers in '142 or '171 to attach albumin to an antibody fragment**

The linkers disclosed in the '142 patent are designed to *link a drug to TTR, not albumin*. Furthermore, the linkers disclosed in the '142 patent are designed to link the drug to TTR *in vivo*. A person skilled in the art would therefore not be motivated to use these linkers for the purpose of covalently attaching albumin to an antibody fragment *in vitro*.

The linkers disclosed in the '171 patent were designed to link a thrombin inhibitor drug to *inter alia* albumin and would not have been considered by the skilled person for linking albumin to an antibody fragment.

3. **No motivation to link antibody fragment site-specifically to albumin**

The '171 patent provides no motivation to link albumin to an antibody fragment via the cysteine at position 34 of albumin. The '171 patent suggests that thiol groups can be used as just one example of various sites of attachment for thrombin drugs to any of the blood components listed but does not go on to use thiol groups in the examples. Instead, amino groups are successfully employed as the site of attachment in the examples. Further, there is *no suggestion that a single thiol group in albumin should be used*. Indeed, in the examples, multiple drugs are attached to each albumin molecule and there is no motivation to conjugate a single drug to a single albumin molecule.

The '142 patent does not disclose preferably *coupling a single drug* to TTR. The '142 patent is concerned with *random* conjugation of drugs to *TTR in vivo*, **not covalent site specific conjugation of antibodies to albumin in vitro.**

The Peters reference would not therefore be considered in combination with the '142 patent or the '171 patent as neither of these references provides any motivation to attach a single antibody fragment to a single cysteine in albumin. Further, the Peters reference would not be

considered in combination with Delgado *et al.* or the '132 patent as neither of these references refer to albumin or even consider it as an alternative to PEG.

In addition, Applicants submit that it was not *prima facie* obvious, as suggested by the Examiner, to couple albumin through the single cysteine at position 34 because the conformation of albumin would remain unchanged. There is simply ***no teaching or suggestion in Peters that linking an antibody fragment to position 34 of albumin using a bridging molecule of from around 10Å to around 20Å would not affect the conformation of the albumin or that the half-life of albumin would be unaffected.***

C. No reasonable expectation of success

The linkers disclosed in United States Patent 5,714,142 and WO 98/00717 were not used to site specifically link the drugs described to albumin at position 34. Accordingly, it would not have been possible to predict whether the linkers described would be suitable for site-specific conjugation of an antibody fragment to albumin at position 34. (Smith Declaration, paragraph 12)

The linkers described in United States Patent 5,714,142 and WO 98/00717 are part of the structure of the drug. That is, the albumin is conjugated to the linker which is already attached to the drug, not vice versa. It would have been impossible to predict whether the same linker once attached to albumin would be incapable of forming homodimers with another albumin molecule. (Smith Declaration, paragraph 13)

The present invention provides an antibody-albumin conjugate in which the antibody fragment is site-specifically bound via a linker of 10-20Å in length to a single cysteine at position 34 of albumin. (Smith Declaration, paragraph 3) Site-specific conjugation ensures that the conjugates produced are homogeneous and thus suitable for therapeutic use. This is in contrast to random conjugation where the sites of attachment can vary each time the conjugate is produced. (Smith Declaration, paragraph 4)

The cysteine at position 34 of albumin had never previously been used as a site of attachment for an antibody fragment. Therefore, it was not known what length or composition of linker would be effective. (Smith Declaration, paragraph 7)

From the crystal structure of albumin it was known that cys 34 is buried in a groove between two helices. This suggested that the cysteine might not be readily accessible to bind a linker. Further, it was not possible to predict how long a linker would be needed to work effectively because the crystal structure does not show how the albumin and the linker behave in solution. Before the present invention, I could not predict whether the linker I had selected would work. (Smith Declaration, paragraph 8)

There were a number of technical questions about the linker that had to be tested experimentally including the following:

- (i) Whether the linker would be long enough to reach the antibody fragment?
- (ii) Whether the linker would also be short enough not to reach another cys 34 in another albumin molecule, i.e. to avoid the formation of albumin homodimers?
- (iii) Whether the linker would be available to bind to the antibody fragment? It was possible that the linker might bind non-covalently to albumin, e.g. within the groove, and therefore not be available for binding to the antibody fragment. (Smith Declaration, paragraph 9)

1. Effect of conjugation on antigen binding was unpredictable

Before the subject invention was made, it could not be predicted whether the antibody fragment would still be capable of binding to its antigen once albumin was attached to the fragment via the linker. There were a number of reasons why antigen binding might have been affected including the following:

- (i) Albumin is known to non-specifically bind to certain proteins and other molecules. It was possible that the albumin would bind to the antibody fragment

and interfere with antigen binding, for example by altering the conformation of the antibody fragment.

- (ii) The antibody Fab' and F(ab')₂ fragments in the examples comprise an antibody hinge region to which the albumin molecule is site specifically attached via the linker. The antibody hinge region is known to be flexible and so it was possible that the albumin could swing around to the antigen binding site and interfere with antigen binding, either directly by binding to the antigen binding site or indirectly for example by binding to the antigen.
 - (iii) It was possible that the mere presence of the albumin and linker attached to the antibody fragment, in particular given the large size of albumin (67kDa), could affect the conformation of the antibody fragment and accordingly antigen binding.
- (Smith Declaration, paragraph 10)

2. Effect of conjugation on Albumin half life was unpredictable

The cysteine at position 34 of albumin is known from the crystal structure to be buried in a groove between two helices. As this was the first attempt to conjugate an antibody fragment to this cysteine I could not predict beforehand what effect this would have on the structure of the albumin and consequently what effect this would have on the half-life of the albumin-antibody conjugate. (Smith Declaration, paragraph 11)

D. Unexpectedly superior advantages of the present invention

The conjugates of the present invention can be produced efficiently. In particular, by using a linker of 10-20Å in length albumin homodimers are not formed and all the albumin molecules with linkers attached are available for conjugation to an antibody fragment. If homodimers were formed these would have to be purified away from the final conjugate, thus reducing efficiency and increasing the cost of production. (Smith Declaration, paragraph 5) The present invention represents a whole new approach to albumin conjugation. Thus, there were a number of technical questions which could only be answered experimentally. Accordingly, at the time the invention was made I did not know whether it would be possible to conjugate an

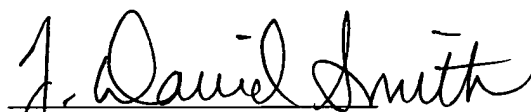
antibody fragment site specifically via a linker to cys 34 of albumin. Even if that were possible, I did not know what effect this would have on antigen binding, albumin conformation and conjugate half-life. (Smith Declaration, paragraph 6)

Conclusion

Applicants believe that the outstanding rejections based on 35 U.S.C. § 103 are improper. Thus, reconsideration and withdrawal of the outstanding grounds of rejection, and early allowance of the claims as amended is believed to be in order and is courteously solicited.

In the event that there are any questions concerning this amendment, or the application in general, the Examiner is respectfully urged to telephone the undersigned at the number listed below, so that prosecution of the application may be expedited.

Respectfully submitted,

A handwritten signature in black ink that reads "J. David Smith". The signature is written in a cursive, flowing style.

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